

Published in final edited form as:

Pediatr Infect Dis J. 2012 March ; 31(3): . doi:10.1097/INF.0b013e31823dcc72.

The Changing Epidemiology of Invasive Pneumococcal Disease at a Tertiary Children's Hospital through the PCV7 Era

KROW AMPOFO, MB, CHB¹, ANDREW T. PAVIA, MD¹, CHRIS STOCKMANN, BSC¹, ADAM L. HERSH, MD, PHD¹, JEFFERY M. BENDER, MD², ANNE J. BLASCHKE, MD, PHD¹, HSIN YI CINDY WENG, MS¹, KENT E. KORGESKI, MS^{1,3}, JUDY DALY, PHD^{1,3}, EDWARD O. MASON, PHD⁴, and CARRIE L. BYINGTON, MD¹

¹Division of Pediatric Infectious Diseases, Department of Pediatrics, University of Utah Health Sciences Center, Los Angeles, CA

²Kaiser Permanente Pediatrics, Los Angeles, CA

³Primary Children's Medical Center, Intermountain Health Care, Salt Lake City, UT

⁴Baylor College of Medicine, Houston, TX

Abstract

Background—In 2000, a 7-valent pneumococcal conjugate vaccine (PCV7) was licensed for use among U.S. children. Many sites have since reported changes in invasive pneumococcal disease (IPD). We recognized an opportunity to describe the changes in epidemiology, clinical syndromes and serotype distribution over a 14 year period including 4 years before vaccine introduction and spanning the entire PCV7 era.

Methods—Cases were defined as children <18 years of age who were cared for at Primary Children's Medical Center for culture-confirmed IPD. We defined the pre-vaccine period as the timeframe spanning 1997–2000 and the post-vaccine period from 2001–2010. Demographics, clinical data, and outcomes were collected through electronic query and chart review. *S. pneumoniae* serotyping was performed using the capsular swelling method.

Results—The median age of children with IPD increased from 19 months during the pre-vaccine period to 27 months during post-vaccine period ($P=0.02$) with a larger proportion of IPD among children older than 5 years. The proportion of IPD associated with pneumonia increased substantially from 29% to 50% ($P<0.001$). This increase was primarily attributable to an increase in complicated pneumonia (17% to 33%; $P<0.001$). Non-vaccine serotypes 7F, 19A, 22F and 3 emerged as the dominant serotypes in the post-vaccine period. Of *S. pneumoniae* isolates collected from children <5 years of age, for which vaccine is recommended, 67% of IPD was due to serotypes in PCV13 during 2005–2010.

Corresponding Author: Krow Ampofo, MB, ChB., Associate Professor, Division of Pediatric Infectious Disease and Geographic Medicine, University of Utah Health Sciences Center, 295 Chipeta Way, 2S010, Salt Lake City, UT 84108, ph 801-581-6791, fax 801-585-3789, Krow.Ampofo@hsc.utah.edu.

Conflict of Interest: None

Disclosures: The authors have no conflicts of interest to disclose. Financial support is provided by grants from the National Institute of Allergy and Infectious Diseases (U01A1082482) (to KA, CLB), (U01 AI074419-01) (to CLB, AJB, ATP), (U01AI082184-01) (to ATP, AJB), 1K23-AI079401-01A1 (to AJB), National Institute of Child Health and Human Development (K-24 HD047249-01A1) (to CLB) and the Centers for Disease Control Prevention (U18-IP000303-01) (to KA, CLB, ATP, AJB). This project was further supported by the University of Utah, Department of Pediatrics through the Children's Health Research Center and the Pediatric Clinical and Translational Research Scholars Program, the H. A. and Edna Benning Presidential Endowment, and the Primary Children's Medical Center Foundation.

Conclusions—After PCV7 was introduced, significant changes in IPD were noted. One third of IPD occurred in children older than 5 years, who were outside the age group for which PCV is recommended. Continued surveillance is warranted to identify further evolution of the epidemiology, clinical syndromes, and serotype distribution of *S. pneumoniae* following PCV13 licensure.

Keywords

Streptococcus pneumoniae; Invasive pneumococcal disease; Serotype; PCV7; PCV13

BACKGROUND

In 2000, a 7-valent pneumococcal conjugate vaccine (PCV7 [Prevnar]; Wyeth Lederle Vaccine) was licensed for use in young children in the United States (U.S.). With increasing use of PCV7 in the U.S.,¹ the epidemiology of invasive pneumococcal disease (IPD) has changed significantly. The Centers for Disease Control and Prevention (CDC) active bacterial core (ABC) surveillance sites report the incidence of IPD in children younger than 5 years decreased more than 70% from 95 cases/100,000 population in 1999 to 23 cases/100,000 population in 2004.² However, these changes have been heterogeneous, with some centers in the U.S. and other regions of the world reporting less dramatic decreases, and the early emergence of IPD due to non-PCV7 serotypes.^{2–7} The causes of the heterogeneous impact of PCV7 remain unknown.

To further protect children against IPD, including IPD caused by emerging *S. pneumoniae* serotypes, a 13-valent pneumococcal conjugate vaccine (PCV13; Wyeth/Pfizer Pharmaceuticals Inc.), with antigens representing 6 of the serotypes that emerged following licensure of PCV7, was licensed for use in children in the U.S. in February 2010.⁸ The objective of this study was to review the epidemiology and serotypes of culture-confirmed IPD in hospitalized children using laboratory-based surveillance at Primary Children's Medical Center (PCMC), in Salt Lake City, Utah, from the pre-PCV7 period through the eve of the introduction of PCV13.

METHODS

Human Subjects Protection

The institutional review boards of the University of Utah, PCMC and Intermountain Healthcare (Intermountain) approved this study with a waiver of informed consent.

Setting and Study Population

PCMC, an Intermountain hospital, is the only children's hospital in the intermountain west region of the U.S. In addition to Utah, PCMC receives referrals from Idaho, Wyoming, Nevada, and Montana. PCMC also serves as a community pediatric hospital for Salt Lake County, Utah. Over the study period, hospital admissions to PCMC increased from 6,418 in 1997 to 9,824 in 2010 with a peak of 10,268 in 2009 associated with the H1N1 pandemic. Over the study period, the catchment area for PCMC has not changed, though the population of the intermountain west has grown significantly.

The study period spanned January 1997 to December 2010. We defined three time periods for analysis based on levels of PCV7 coverage. The pre-vaccine period was the 48-month period from January 1997 through December 2000, preceding PCV7 licensure in the U.S. We defined the early vaccine period as the 48 months from January 2001 to December 2004, when PCV7 uptake (> 3 doses) was increasing but coverage was less than 80% for children younger than 36 months. The late vaccine period included the 72 months from January 2005

to December 2010 when PCV7 coverage was greater than 80% for children in Utah. For some analyses, we combined 2001–2010 as the post-vaccine period. Vaccine coverage rates for PCV7 in Utah as determined by the National Immunization Survey were similar to those reported nationally.¹ Immunization status was assessed on the basis of the CDC's Advisory Committee on Immunization Practices (ACIP) recommendations.⁹

Identification of Culture-confirmed *S. pneumoniae* Infection

Culture-confirmed IPD cases were defined as children younger than 18 years with *S. pneumoniae* isolated from a normally sterile site (e.g. blood, cerebrospinal fluid, joint, pleural, or peritoneal fluid, or abscess). PCMC laboratory staff have archived all pneumococcal isolates from children with IPD since 1996. *S. pneumoniae* serotyping was performed at Baylor College of Medicine (EOM) using the capsular swelling method as previously described.³ Demographic, clinical information and chronic medical conditions predisposing to IPD and antimicrobial susceptibilities of IPD isolates were abstracted from electronic medical records using Intermountain's Enterprise Data Warehouse.

In 2008, Clinical and Laboratory Standards Institute (CLSI formerly National Committee for Clinical Laboratory Standards), published new breakpoints for parenteral penicillin for *S. pneumoniae* from non-meningeal and meningeal sites.¹⁰ For this study and similar to a previous study,¹¹ all *S. pneumoniae* penicillin and cefotaxime breakpoints used were those for parenteral non-meningeal infections regardless of the site of isolation. Thus, we defined isolates as penicillin susceptible if the MIC was ≤ 2.0 mcg/mL and cefotaxime susceptible if the MIC was ≤ 1 mcg/mL.¹⁰ From 1997 to 2003 antimicrobial susceptibility to penicillin and cefotaxime was determined using the Kirby-Bauer disc diffusion method (AB Biodisk, Solna, Sweden). From 2004 through 2007, susceptibility testing was performed by the epsilometric test (E-test) and since 2008, by the MICroSTREP microtiter method (Seimens Healthcare Diagnostics, West Sacramento, CA).

Statistical Analyses

Descriptive statistics were used to summarize the demographic and clinical characteristics of cases. Rates and proportions were compared using chi square or Fisher exact tests as appropriate. The Mann-Whitney *U* test was used to perform pairwise comparisons of continuous variables. All reported *P* values are 2-sided. Statistical analyses were performed using Stata 11.2 (StataCorp LP, College Station, TX, USA).

RESULTS

Demographics and Underlying Medical Conditions

During the study period, 513 children with culture-confirmed IPD who were cared for at PCMC were identified. Males were overrepresented in both the pre-vaccine and vaccine periods (59% and 60%, respectively). The median age of children with IPD increased from 19 months during the pre-vaccine era to 27 months during the post-vaccine era ($P = 0.02$). In the pre-vaccine era, the majority of children with IPD (54%) were younger than 2 years of age, 27% were between 2 and 4 years, and 20% were older than 5. The proportion of children with IPD younger than 2 years decreased after PCV7 introduction (54% vs. 43%, $P = 0.03$) and the proportion of disease among children 5 years or older increased (20% vs. 28%, $P = 0.06$) (Table 1).

There was an increase in the proportion of children with IPD who had one or more underlying chronic medical conditions (1.6% during the pre-vaccine period vs. 7.5% in the vaccine period, $P = 0.01$). The most common chronic medical condition was cardiac disease

($n = 13$), followed by neuromuscular disorders ($n = 10$). Immune-compromising conditions were noted more frequently in the vaccine era (14.5% vs. 5.5%, $P < 0.01$).

Of 385 children with IPD during the vaccine period, immunization records were available for 338 (88%). Of these, 163 (48%) received 1 dose of PCV7. Per ACIP recommendations, 96 (28%) children were fully immunized with PCV7. Following approval of PCV13 in February of 2010, 35 children developed IPD and 33 (94%) had vaccine records available for review. Prior to hospital admission, 2 (6%) children received 1 dose of PCV13.

Outcomes and Antimicrobial Susceptibilities of Culture-Confirmed IPD

Outcomes among children with IPD were similar in the pre-vaccine and vaccine periods. Similar proportions were admitted to the intensive care unit (ICU) (41% pre-vaccine period vs. 35% vaccine period, $P = 0.3$) and the case-fatality rate (4.5%) was similar during the pre-vaccine and vaccine periods. However, among children two years of age and older, the proportion requiring intensive care admission declined from 44% in the pre-vaccine period to 30% in the vaccine period ($P = 0.04$).

S. pneumoniae isolates not susceptible to penicillin and cefotaxime decreased over the study period (Table 1). Rates of antimicrobial non-susceptibility varied by serotype, with the highest rates of penicillin (64%) and cefotaxime (24%) resistance among serotype 19A.

Clinical Syndromes of IPD

The distribution of clinical syndromes associated with IPD changed substantially by the study period (Figure 1). In the pre-vaccine era, bacteremia without focus (37%) was the most frequent cause of IPD, while complicated pneumonia (33%) was most frequent during the vaccine period. The proportion of cases attributable to bacteremia without focus declined from 47/128 (37%) in the pre-vaccine period to 95/385 (25%) in the vaccine period ($P = 0.02$). The proportion due to meningitis and musculoskeletal disease remained stable across the two study periods. The proportion of IPD associated with pneumonia increased significantly from 37/128 (29%) to 191/385 (50%) ($P < 0.001$). This increase was primarily attributable to an increase in complicated pneumonia (pneumonia complicated by parapneumonic effusion, empyema, necrotizing lung, or lung abscesses). Between the pre-vaccine period and the vaccine period, the proportion of all IPD due to complicated pneumonia increased from 22/128 (17%) to 127/385 (33%) ($P < 0.001$) (Table 1).

Children with meningitis were significantly younger (median age 9 months vs. 25 months; $P < 0.001$) than other children with IPD, and those with complicated pneumonia were significantly older during both study periods (median age 37 months vs. 25 months; $P < 0.001$). The median age of children with IPD and uncomplicated pneumonia increased from 15 months in the pre-vaccine period to 31 months during the vaccine period ($P = 0.07$).

Distribution of *S. pneumoniae* Serotypes

The distribution of *S. pneumoniae* serotypes causing IPD in Utah changed significantly between the pre-vaccine and vaccine periods. The proportion of IPD caused by PCV7 serotypes declined dramatically and continued to decline following introduction of PCV7 in 2000 (59% vs. 15%, $P < 0.001$) (Figure 2). Between 2001 and 2010, the proportion of disease caused by non-PCV7 serotypes increased significantly (41% vs. 85%, $P < 0.001$). The increase was driven initially by the emergence of serotypes 3 and 19A followed by increase in serotypes 7F, 19A, 22F, and 3 during the late vaccine period (2005–2010) (Figure 3).

Serotype 7F was the most frequent cause of IPD during the vaccine period, accounting for 72/385 cases (19%), followed by serotype 19A (62/385 isolates [16%]). These predominantly increased between 2005 and 2010 (Figure 3). More than half of serotype 7F (38/72 [53%]) isolates were from patients with pneumonia (Table 1). Eighteen of 72 (25%) children with serotype 7F infection required ICU admission but death was infrequent (1%). Fifty one percent of serotype 7F isolates were from children younger than 2 years of age compared to 41% of other serotypes ($P = 0.1$) (Table 1).

The majority (55%) of the cases of IPD caused by serotype 19A were associated with pneumonia. Rates of ICU admission (26%) and death (5%) associated with serotype 19A were not different from other serotypes (Table 1).

Serotype 3 increased rapidly in the early vaccine period, and remained stable thereafter (Figure 3). Seventy-five percent of all serotype 3 infections were associated with complicated pneumonia. Patients with serotype 3 were more likely to be admitted to ICU than patients with other serotypes during the post vaccine era ($P = 0.04$) (Table 1).

Serotype 22F, a serotype not included in PCV 13, increased during the late vaccine period. Almost 22% of 22F isolates were from patients with meningitis compared to 12% of all other isolates ($P < 0.001$).

Serotype 1, a relatively common serotype among Utah children before licensure of PCV7, remained stable over time (Figure 3). During the vaccine period, children with serotype 1 infection were older than children with infection caused by other serotypes (median 48 months compared to 27 months; $P = 0.04$). The majority of cases of IPD caused by serotype 1 were pneumonia (93%). Serotype 1 was also strongly associated with complicated pneumonia when compared with other serotypes (86% vs. 29%; OR 14.0; $P < 0.001$) (Table 1).

During the vaccine period, clinical syndromes of IPD varied by serotype and outcome (Table 1). Cases of complicated pneumonia were predominantly caused by *S. pneumoniae* serotype 1 (20%) and emerging serotypes 7F (19%), 19A (17%), and 3 (17%). Meningitis was frequently associated with serotypes 22F and 7F. Thirty-nine of 49 (80%) meningitis cases required ICU admission and 12% died. Penicillin and cefotaxime non-susceptibility were highest among meningitis cases (24% and 29%, respectively).

From 2005–2010, 67% of all IPD cared for at PCMC was due to pneumococcal serotypes contained in PCV13 (Figure 3). The proportion was similar (67%) in children younger than 5 years, the target group for PCV13. A total of 53% of meningitis, 60% of bacteremia without focus, 64% of uncomplicated pneumonia, and 80% of complicated pneumonia isolates during the late-vaccine period (2005–2010) were PCV13 serotypes.

DISCUSSION

We evaluated changes in *S. pneumoniae* serotypes and clinical syndromes in children with IPD at a children's hospital in Utah, spanning 4 years before and 10 years after licensure of PCV7. After the introduction and widespread use of PCV7 in Utah, we observed a shift in culture-confirmed IPD to older children with an increase in the median age from 18 months to 27 months. The shift was primarily due to a decrease in IPD among children younger than 2 years and an increase among children older than 5 years. There has been a differential effect of PCV7 on the clinical syndromes associated with IPD. Bacteremia without focus declined while complicated pneumonia increased substantially. Invasive infection with PCV7 serotypes was virtually eliminated, offset by an increase in emerging non-PCV7 serotypes, especially serotypes 7F, 19A, 22F and 3. Non-susceptibility to penicillin and

cefotaxime decreased rapidly, and remains lower, despite the emergence of resistant strains of serotype 19A.

Since the introduction of PCV7, studies in a variety of settings have shown a decrease in IPD in all age groups.^{12,13} The largest declines in IPD were among the vaccine target group (< 5 years of age), and in adults and the elderly, presumably as a result of herd immunity.^{4,12,14} Similarly, we recently reported significant declines in the incidence of IPD in Utah children < 2 years and 2 to < 5 years, with no change among those 5 to 17 years.¹⁵ It is of note that the emergence of non-PCV7 serotypes has been associated with a shift to a greater proportion of IPD occurring in older children. We observed increases in the age of children with bacteremia without focus and pneumonia (both complicated and uncomplicated). Chibuk et al noted a similar increase in the age of children with complicated pneumonia in Canada.¹⁶ In contrast Li et al, using U.S. hospital discharge data, reported a decrease in the age of children hospitalized with empyema from 7.3 years to 6.3 years between 1997 and 2006.¹⁷ These findings have implications for identifying the optimal age for use of PCV13. It will be critical to determine if using the vaccine exclusively in children younger than 5 will translate into a decrease in IPD in older children.

We observed an increase in the proportion of children with underlying chronic medical conditions from 1.6% in the pre-vaccine period to 7.5% during the vaccine period. Our findings are supported by results from a case-control study evaluating the effectiveness of PCV7 against IPD, using data from the CDC's ABC surveillance sites.¹⁸ Among healthy children, the effectiveness of 1 dose of PCV7 against vaccine serotypes was 96% (95% CI: 93–98), while among children with chronic medical conditions, PCV7 vaccine effectiveness was significantly lower at 81% (95% CI: 57–92) ($P = 0.001$). In another study, Park et al. demonstrated that vaccine-serotype IPD occurred 2.8 times more frequently among children with an identified chronic medical condition, when compared to non-vaccine serotype IPD (95% CI: 1.3–6.1) among children who had received 1 dose of PCV7.¹⁹ Together, these data support the finding that PCV7 is less effective among children with chronic medical conditions. In our study, the proportion of immune-compromising conditions increased 3-fold by the vaccine period. A report from South Africa demonstrated decreased efficacy of the 9-valent pneumococcal conjugate vaccine among HIV-infected children,²⁰ and it is likely that among children with congenital and acquired immunodeficiency syndromes, protective immunity after PCV7 vaccination is lower than among healthy children.

The epidemiology of IPD varies significantly by geographic region.²¹ Ongoing surveillance of IPD at the CDC's ABC sites through 2007 noted increases in infection with non-PCV7 serotypes in all sites, with significant increases in serotypes 19A, 15, 33F, 22F, 3 and 5.^{2,21,22} In Massachusetts, infections with serotype 19A increased from 10% of IPD in 2002 to 41% in 2006.²³ In our study, serotypes 7F, 19A, 3, and 22F have increased and collectively account for 49% of IPD in the vaccine period. The largest increase was serotype 7F, which predominantly emerged in the later years of the study. After 2005, serotype 7F has been the leading cause of bacteremia without focus, meningitis and both uncomplicated and complicated pneumonia. Serotype 19A emerged in the early vaccine period. In many regions of the U.S. serotype 19A has become the most common serotype since the licensure of PCV7.^{2,11,24–26} However in our population, serotype 7F has surpassed 19A and accounted for 20% of meningitis cases. Serotype 22F, a serotype not included in PCV13 increased considerably in the late vaccine period and represented 6% of all IPD and 10% of meningitis. Other recent studies have reported the increasing role of serotype 22F in meningitis.^{22,27} In our study, serotypes 1 (86%) and 3 (75%) were strongly associated with complicated pneumonia, consistent with previous reports.^{5,28–31}

The recently licensed PCV13 targets several of the common non-vaccine serotypes that have emerged in the U.S. By the late vaccine period (2005–2010), 64% of isolates from children < 18 years and 59% of isolates from children < 5 years in our study were serotypes contained in PCV13. Our findings are similar to those of Pilishvili et al, who report that 68% of IPD among children <5 years in the ABC sites during the 2006–2007 season was due to PCV13 serotypes.³² Interestingly, when specific clinical syndromes were evaluated, the proportion of disease due to PCV13 serotypes varied significantly. PCV13 serotypes were responsible for 85% of complicated pneumonia but only 55% of meningitis from the late vaccine period (2005–2010). Thus the introduction of PCV13 may impact specific IPD clinical syndromes differently.⁸

The widespread use of PCV7 was associated with a significant decrease in the proportion of penicillin and cefotaxime non-susceptible *S. pneumoniae*, in agreement with previous reports.^{2–4,12,22,33} Reductions in nasopharyngeal colonization of penicillin non-susceptible PCV7 isolates previously associated with IPD, and colonization by non-PCV7 serotype which have generally been susceptible likely contributed to the overall increase in susceptibility of *S. pneumoniae* to penicillin and cefotaxime.^{34,35} Decreases in antibiotic prescribing for outpatients with upper respiratory infections may be another factor.³⁵ However, the emergence of multidrug resistant clones of serotype 19A poses a threat to these gains in Utah and other regions.^{25,36–38} A mathematical model predicted the development of resistance in emerging *S. pneumoniae* serotypes with sustained antibiotic use that could reverse the gains of PCV7.³⁹ Thus, vaccine use must be coupled with more prudent use of antibiotics to control antimicrobial resistance among *S. pneumoniae*.

This study has a number of limitations. First, it is based in a single geographic area, and pneumococcal epidemiology is known to have substantial regional variation. However our findings are generally in accordance with reports from other parts of North America and Europe.^{2,4,12} Second, vaccination records were available for a majority of children with IPD (88%); however, they were not available for all children. Lastly, like many other studies, serotyping was only performed on patients with viable isolates, which represent a modest proportion of all patients with IPD. Antibiotic pre-treatment, the low rate of bacteremia in pneumococcal pneumonia and the tendency of *S. pneumoniae* for autolysis limit the recovery and may bias the serotype distribution. We have demonstrated differences in serotype distribution in pleural fluid samples when molecular methods are employed and future surveillance studies may produce a more complete picture of serotype distribution in IPD if molecular methods can be employed in addition to culture.⁴⁰

In summary, PCV7 vaccination has had a differential effect on *S. pneumoniae* serotypes, age distribution, clinical syndromes, and antibiotic susceptibilities in Utah. After vaccine introduction, children with IPD in Utah were older. Up to a third of IPD occurred in children older than 5 years, outside the age group for which PCV is recommended. Non-PCV7 serotypes 7F, 19A, 22F, 3 and 1 have emerged as the dominant serotypes, and complicated pneumonia has increased. At the time of licensure of PCV13, ~70% of IPD was due to serotypes in PCV13. The changes in *S. pneumoniae* epidemiology in children and adults after the introduction of PCV7 have been complex and not completely understood. Similar complex changes are likely to evolve as PCV13 coverage increases. Continued surveillance is essential to identify further evolution of the epidemiology, clinical syndromes and serotype distribution of invasive *S. pneumoniae* disease in order to optimize prevention strategies.

Acknowledgments

Financial Support

Supported by grants from the National Institute of Allergy and Infectious Diseases (U01A1082482) (to KA, CLB), (U01 A1074419-01) (to CLB, AJB, ATP), (U01A1082184-01) (to ATP, AJB), 1K23-AI079401-01A1 (to AJB), National Institute of Child Health and Human Development (K-24 HD047249-01A1) (to CLB) and the Centers for Disease Control Prevention (U18-IP000303-01) (to KA, CLB, ATP, AJB). This project was further supported by the University of Utah, Department of Pediatrics through the Children's Health Research Center and the Pediatric Clinical and Translational Research Scholars Program, the H. A. and Edna Benning Presidential Endowment, and the Primary Children's Medical Center Foundation.

PCMC microbiology laboratory for storing and archiving *S. pneumoniae* isolates and Intermountain Healthcare, Salt Lake City, Utah.

References

1. [Accessed May 13, 2009] Statistics and Surveillance: Immunization Coverage in the US. 2009. (<http://www.cdc.gov/vaccines/stats-surv/imz-coverage.htm#nis>)
2. Hicks LA, Harrison LH, Flannery B, et al. Incidence of Pneumococcal Disease Due to Non-Pneumococcal Conjugate Vaccine (PCV7) Serotypes in the United States during the Era of Widespread PCV7 Vaccination, 1998–2004. *J Infect Dis*. 2007; 196:1346–54. [PubMed: 17922399]
3. Byington CL, Samore MH, Stoddard GJ, et al. Temporal trends of invasive disease due to *Streptococcus pneumoniae* among children in the intermountain west: emergence of nonvaccine serogroups. *Clin Infect Dis*. 2005; 41:21–9. [PubMed: 15937758]
4. Singleton RJ, Hennessy TW, Bulkow LR, et al. Invasive pneumococcal disease caused by nonvaccine serotypes among alaska native children with high levels of 7-valent pneumococcal conjugate vaccine coverage. *Jama*. 2007; 297:1784–92. [PubMed: 17456820]
5. Eastham KM, Freeman R, Kearns AM, et al. Clinical features, aetiology and outcome of empyema in children in the north east of England. *Thorax*. 2004; 59:522–5. [PubMed: 15170039]
6. Obando I, Arroyo LA, Sanchez-Tatay D, Moreno D, Hausdorff WP, Brueggemann AB. Molecular typing of pneumococci causing parapneumonic empyema in Spanish children using multilocus sequence typing directly on pleural fluid samples. *Pediatr Infect Dis J*. 2006; 25:962–3. [PubMed: 17006306]
7. Spratt BG, Greenwood BM. Prevention of pneumococcal disease by vaccination: does serotype replacement matter? *Lancet*. 2000; 356:1210–1. [PubMed: 11072934]
8. Licensure of a 13-Valent Pneumococcal Conjugate Vaccine (PCV13) and Recommendations for Use Among Children --- Advisory Committee on Immunization Practices (ACIP), 2010. *MMWR Morb Mortal Wkly Rep*. 2010; 59:258–61. [PubMed: 20224542]
9. Centers for Disease Control and Prevention. Preventing pneumococcal disease among infants and young children: recommendations of the Advisory Committee on Immunization Practices. *MMWR*. 2000; 49(RR-9):1–38.
10. Clinical and Laboratory Standards Institute/NCCLS. CLSI/NCCLS document M100-S18. Clinical and Laboratory Standards Institute; Wayne, PA, USA: 2008. Performance standards for antimicrobial susceptibility testing; eighteenth informational supplement.
11. Techasaensiri C, Messina AF, Katz K, Ahmad N, Huang R, McCracken GH Jr. Epidemiology and evolution of invasive pneumococcal disease caused by multidrug resistant serotypes of 19A in the 8 years after implementation of pneumococcal conjugate vaccine immunization in Dallas, Texas. *Pediatr Infect Dis J*. 2010; 29:294–300. [PubMed: 19949357]
12. Whitney CG, Farley MM, Hadler J, et al. Decline in invasive pneumococcal disease after the introduction of protein-polysaccharide conjugate vaccine. *N Engl J Med*. 2003; 348:1737–46. [PubMed: 12724479]
13. Simonsen L, Taylor RJ, Young-Xu Y, Haber M, May L, Klugman KP. Impact of pneumococcal conjugate vaccination of infants on pneumonia and influenza hospitalization and mortality in all age groups in the United States. *MBio*. 2011;2.
14. Hammit LL, Bruden DL, Butler JC, et al. Indirect effect of conjugate vaccine on adult carriage of *Streptococcus pneumoniae*: an explanation of trends in invasive pneumococcal disease. *J Infect Dis*. 2006; 193:1487–94. [PubMed: 16652275]
15. Ampofo K, Pavia AT, Stockmann C, et al. Evolution of the Epidemiology of Pneumococcal Disease among Utah Children through the Vaccine Era. *Pediatr Infect Dis J*. 2011 In press.

16. Chibuk TK, Robinson JL, Hartfield DS. Pediatric complicated pneumonia and pneumococcal serotype replacement: trends in hospitalized children pre and post introduction of routine vaccination with Pneumococcal Conjugate Vaccine (PCV7). *Eur J Pediatr*. 2010; 169:1123–8. [PubMed: 20383524]
17. Li ST, Tancredi DJ. Empyema hospitalizations increased in US children despite pneumococcal conjugate vaccine. *Pediatrics*. 2010; 125:26–33. [PubMed: 19948570]
18. Whitney CG, Pilishvili T, Farley MM, et al. Effectiveness of seven-valent pneumococcal conjugate vaccine against invasive pneumococcal disease: a matched case-control study. *Lancet*. 2006; 368:1495–502. [PubMed: 17071283]
19. Park SY, Van Beneden CA, Pilishvili T, Martin M, Facklam RR, Whitney CG. Invasive pneumococcal infections among vaccinated children in the United States. *J Pediatr*. 2010; 156:478–83. e2. [PubMed: 19962156]
20. Klugman KP, Madhi SA, Huebner RE, Kohberger R, Mbelle N, Pierce N. A trial of a 9-valent pneumococcal conjugate vaccine in children with and those without HIV infection. *N Engl J Med*. 2003; 349:1341–8. [PubMed: 14523142]
21. Rosen JB, Thomas AR, Lexau CA, et al. Geographic variation in invasive pneumococcal disease following pneumococcal conjugate vaccine introduction in the United States. *Clin Infect Dis*. 2011; 53:137–43. [PubMed: 21690620]
22. Hsu HE, Shutt KA, Moore MR, et al. Effect of pneumococcal conjugate vaccine on pneumococcal meningitis. *N Engl J Med*. 2009; 360:244–56. [PubMed: 19144940]
23. Emergence of antimicrobial-resistant serotype 19A *Streptococcus pneumoniae*--Massachusetts, 2001–2006. *MMWR Morb Mortal Wkly Rep*. 2007; 56:1077–80. [PubMed: 17947966]
24. Pai R, Moore MR, Pilishvili T, Gertz RE, Whitney CG, Beall B. Postvaccine genetic structure of *Streptococcus pneumoniae* serotype 19A from children in the United States. *J Infect Dis*. 2005; 192:1988–95. [PubMed: 16267772]
25. Moore MR, Gertz RE Jr, Woodbury RL, et al. Population snapshot of emergent *Streptococcus pneumoniae* serotype 19A in the United States, 2005. *J Infect Dis*. 2008; 197:1016–27. [PubMed: 18419539]
26. Kaplan SL, Barson WJ, Lin PL, et al. Serotype 19A Is the most common serotype causing invasive pneumococcal infections in children. *Pediatrics*. 2010; 125:429–36. [PubMed: 20176669]
27. Jacobs MR, Good CE, Bajaksouzian S, Windau AR. Emergence of *Streptococcus pneumoniae* serotypes 19A, 6C, and 22F and serogroup 15 in Cleveland, Ohio, in relation to introduction of the protein-conjugated pneumococcal vaccine. *Clin Infect Dis*. 2008; 47:1388–95. [PubMed: 18959493]
28. Bender JM, Ampofo K, Korgenski K, et al. Pneumococcal necrotizing pneumonia in Utah: does serotype matter? *Clin Infect Dis*. 2008; 46:1346–52. [PubMed: 18419434]
29. Muñoz-Almagro C, Jordan I, Gene A, Latorre C, Garcia-Garcia JJ, Pallares R. Emergence of Invasive Pneumococcal Disease Caused by Nonvaccine Serotypes in the Era of 7-Valent Conjugate Vaccine. *Clinical Infectious Diseases*. 2008; 46:174–82. [PubMed: 18171247]
30. Byington CL, Korgenski K, Daly J, Ampofo K, Pavia A, Mason EO. Impact of the pneumococcal conjugate vaccine on pneumococcal parapneumonic empyema. *Pediatr Infect Dis J*. 2006; 25:250–4. [PubMed: 16511389]
31. Obando I, Munoz-Almagro C, Arroyo LA, et al. Pediatric parapneumonic empyema, Spain. *Emerg Infect Dis*. 2008; 14:1390–7. [PubMed: 18760005]
32. Pilishvili T, Lexau C, Farley MM, et al. Sustained Reductions in Invasive Pneumococcal Disease in the Era of Conjugate Vaccine. *J Infect Dis*. 2010; 201:32–41. [PubMed: 19947881]
33. Talbot TR, Poehling KA, Hartert TV, et al. Reduction in high rates of antibiotic-nonsusceptible invasive pneumococcal disease in tennessee after introduction of the pneumococcal conjugate vaccine. *Clin Infect Dis*. 2004; 39:641–8. [PubMed: 15356776]
34. Dagan R, Givon-Lavi N, Zamir O, Fraser D. Effect of a nonavalent conjugate vaccine on carriage of antibiotic-resistant *Streptococcus pneumoniae* in day-care centers. *Pediatr Infect Dis J*. 2003; 22:532–40. [PubMed: 12799510]
35. Grijalva CG, Nuorti JP, Griffin MR. Antibiotic prescription rates for acute respiratory tract infections in US ambulatory settings. *JAMA*. 2009; 302:758–66. [PubMed: 19690308]

36. Beall BW, Gertz RE, Hulkower RL, Whitney CG, Moore MR, Brueggemann AB. Shifting genetic structure of invasive serotype 19A pneumococci in the United States. *J Infect Dis.* 2011; 203:1360–8. [PubMed: 21398395]
37. Tarrago D, Aguilar L, Garcia R, Gimenez MJ, Granizo JJ, Fenoll A. Evolution of clonal and susceptibility profiles of serotype 19A *Streptococcus pneumoniae* among invasive isolates from children in Spain, 1990 to 2008. *Antimicrob Agents Chemother.* 2011; 55:2297–302. [PubMed: 21343456]
38. Harrison CJ, Woods C, Stout G, Martin B, Selvarangan R. Susceptibilities of *Haemophilus influenzae*, *Streptococcus pneumoniae*, including serotype 19A, and *Moraxella catarrhalis* paediatric isolates from 2005 to 2007 to commonly used antibiotics. *J Antimicrob Chemother.* 2009; 63:511–9. [PubMed: 19174454]
39. Temime L, Boelle PY, Valleron AJ, Guillemot D. Penicillin-resistant pneumococcal meningitis: high antibiotic exposure impedes new vaccine protection. *Epidemiol Infect.* 2005; 133:493–501. [PubMed: 15962556]
40. Blaschke AJ, Heyrend C, Byington CL, et al. Molecular Analysis Improves Pathogen Identification and Epidemiologic Study of Pediatric Parapneumonic Empyema. *Pediatr Infect Dis J.* 2010

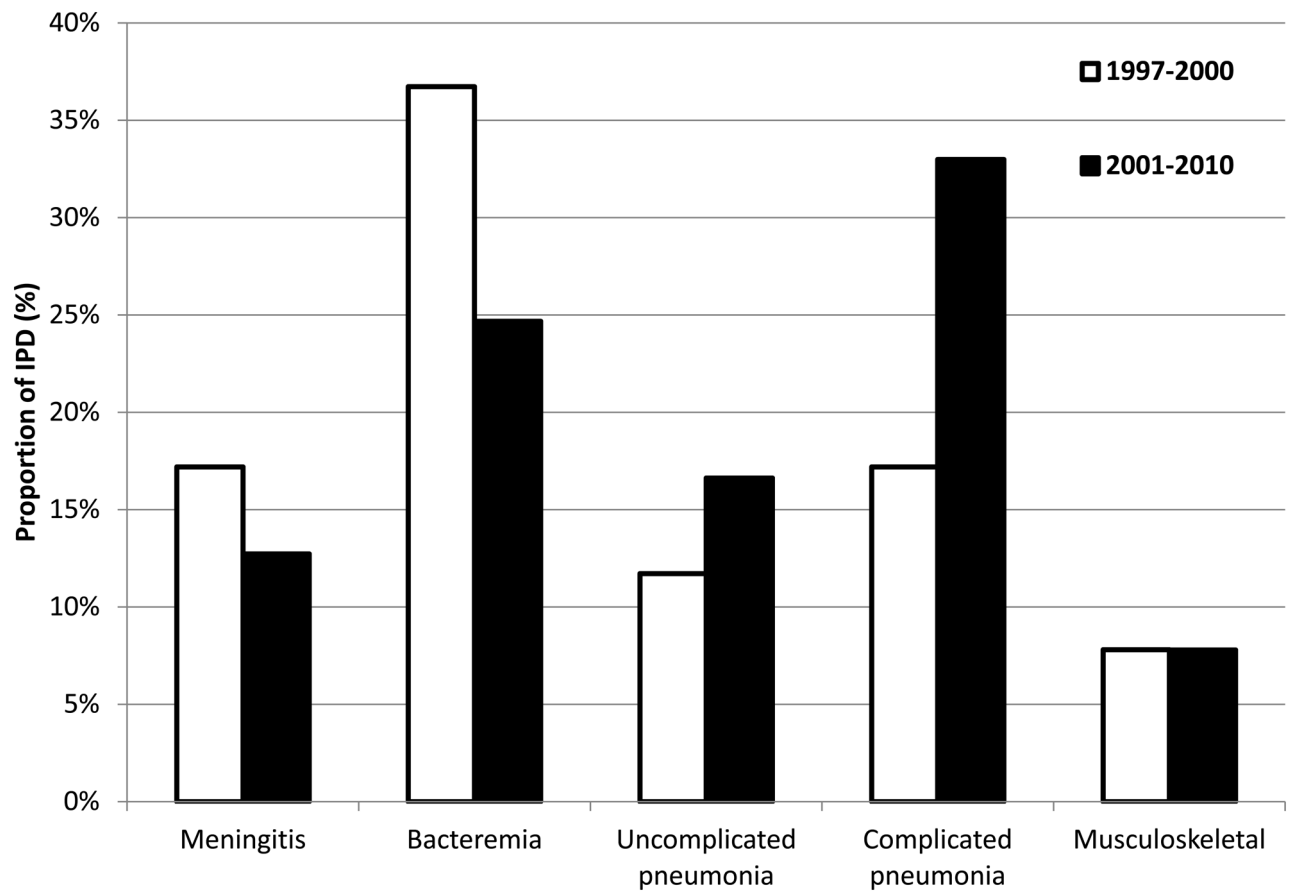


Figure 1.

Proportion of IPD attributed to clinical syndromes in Utah during the pre- (1997–2000) and post- (2001–2010) vaccine periods.

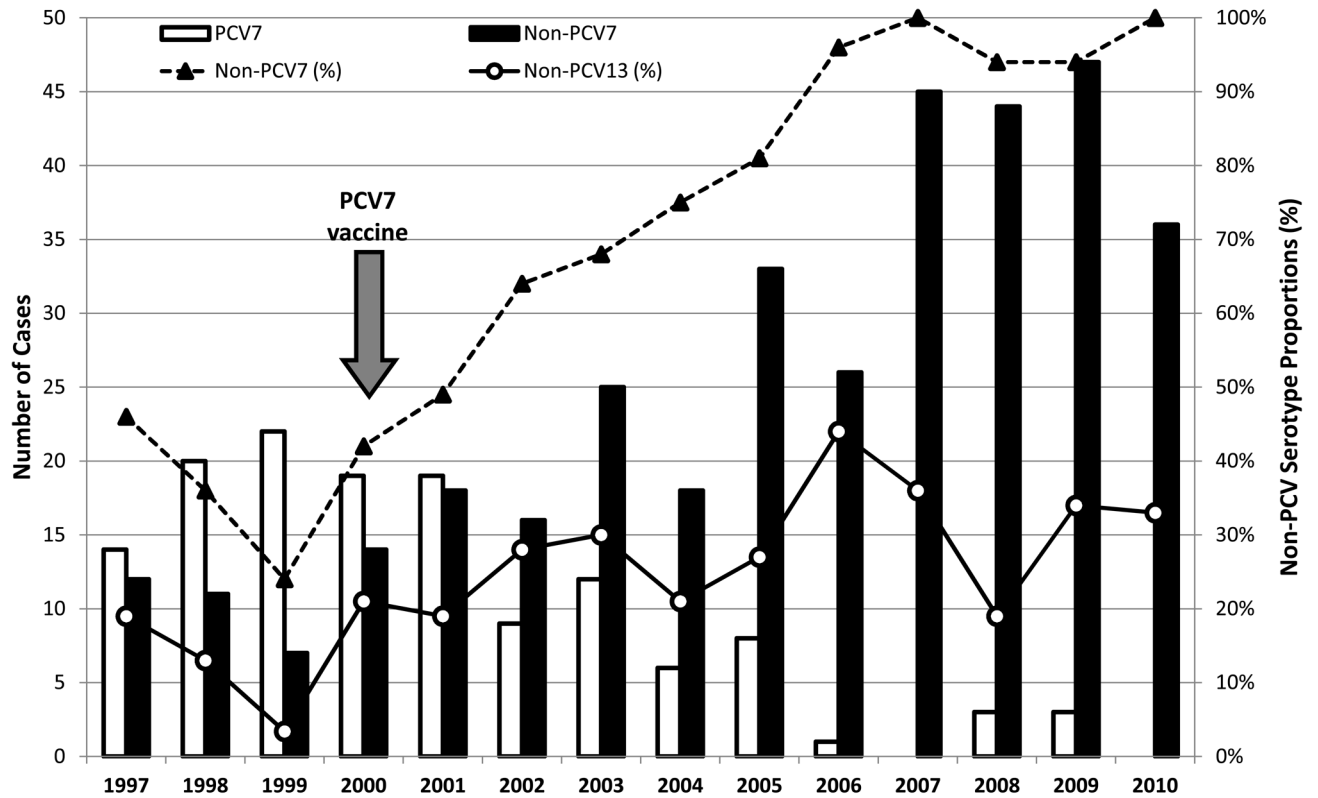
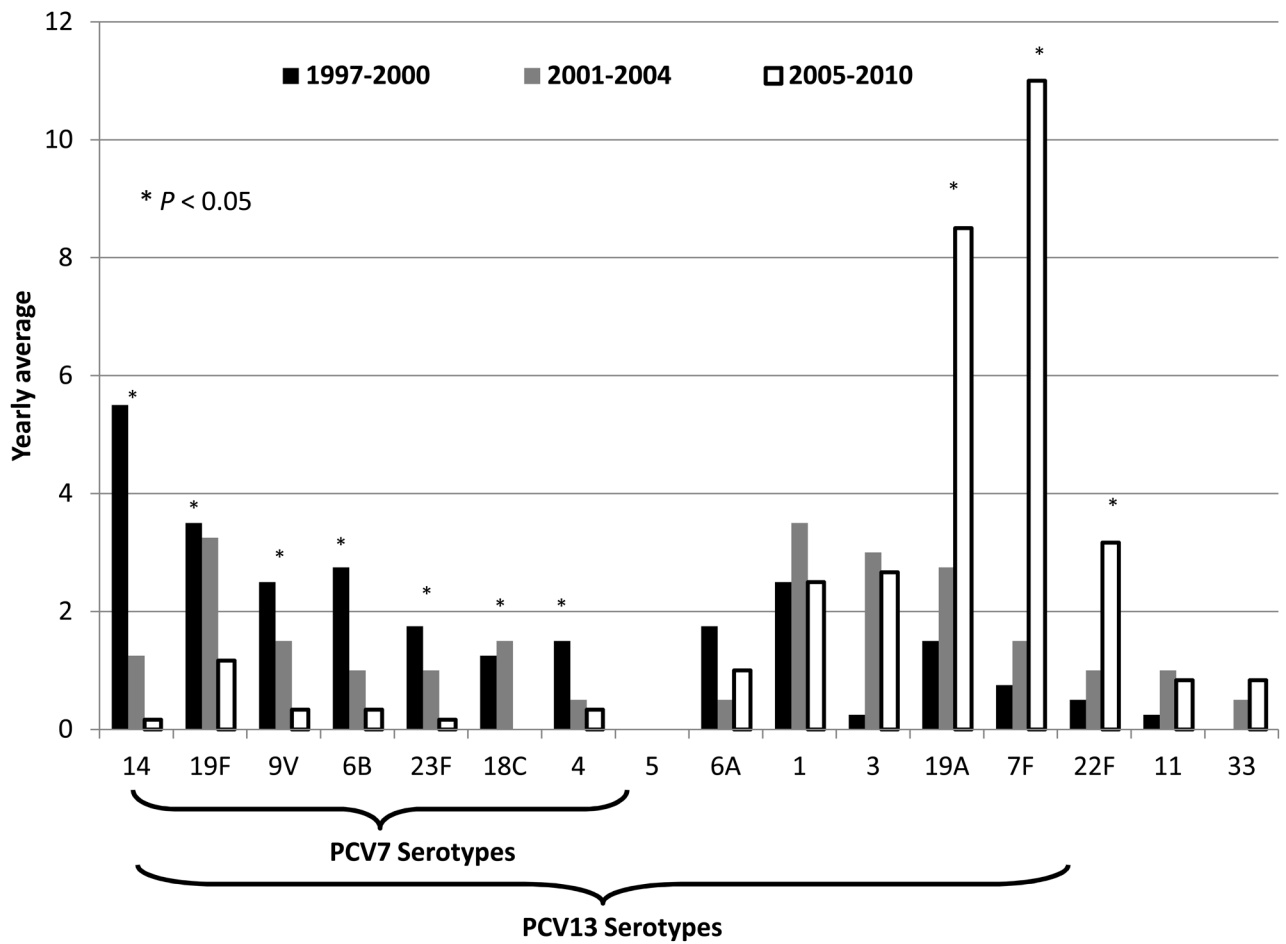


Figure 2.

Number and proportion (%) of PCV versus non-PCV *S. pneumoniae* in children with culture-confirmed IPD at PCMC, Utah, 1997–2000.

**Figure 3.**

Yearly average of *S. pneumoniae* serotypes isolated by PCV7 period among hospitalized children at PCMC, 1997–2010.

Table 1

Clinical characteristics of invasive pneumococcal disease by serotype before (1997–2000) and after (2001–2010) introduction of PCV7.

Variable	1997–2000		2001–2010							
	All Serotypes (N=128)	PCV7 (n=75)	All serotypes (N=385)	PCV7 (n=58)	7F (n=72)	19A (n=62)	1 (n=29)	3 (n=28)	22F (n=23)	Other (n=113)
Age, n (%)										
< 2 years	69 (54)	42 (56)	165 (43)	25 (43)	37 (51)	25 (40)	6 (21)	11 (39)	6 (26)	56 (50)
2 – 4 years	34 (27)	20 (27)	113 (29)	17 (29)	12 (17)	23 (37)	13 (45)	10 (36)	7 (30)	32 (28)
5 – 17 years	25 (20)	13 (17)	107 (28)	16 (28)	23 (32)	14 (23)	10 (35)	7 (25)	10 (44)	28 (25)
Clinical Syndrome, n (%)										
Meningitis	22 (17)	14 (19)	49 (12)	11 (19)	10 (14)	4 (7)	0	2 (7)	5 (22)	17 (15)
Bacteremia	47 (37)	33 (44)	95 (25)	22 (38)	16 (22)	14 (23)	0	2 (7)	6 (26)	35 (31)
All Pneumonia	37 (29)	17 (23)	191 (50)	18 (31)	38 (53)	34 (55)	27 (93)	23 (82)	10 (44)	44 (39)
Uncomplicated	15 (12)	8 (11)	64 (17)	11 (19)	14 (19)	12 (19)	2 (7)	2 (7)	5 (22)	19 (17)
Complicated	22 (17)	9 (12)	127 (33)	7 (12)	24 (33)	22 (36)	25 (86)	21 (75)	5 (22)	25 (22)
Musculoskeletal	10 (8)	5 (7)	30 (8)	6 (10)	6 (8)	7 (11)	0	0	1 (4)	10 (9)
Other	12 (9)	6 (8)	20 (5)	1 (2)	2 (3)	12 (19)	2 (7)	1 (4)	1 (4)	10 (9)
Complication, n (%)										
ICU	53 (41)	29 (39)	131 (35)	21 (36)	18 (25)	16 (26)	10 (35)	15 (54)	7 (30)	45 (40)
Death	6 (5)	4 (5)	17 (5)	2 (3)	1 (1)	3 (5)	1 (3)	0	0	10 (9)
Antibiotic susceptibility, n (%)										
Penicillin	84 (66)	44 (59)	286 (76)	40 (69)	62 (86)	22 (36)	28 (97)	28 (100)	22 (96)	86 (76)
Cefotaxime	84 (66)	44 (59)	341 (90)	51 (88)	69 (96)	47 (76)	28 (97)	26 (93)	21 (91)	100 (89)